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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/817,507	04/17/1997	TADAMITSU KISHIMOTO	53466/201	8301

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/817,507	KISHIMOTO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15 and 24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/15/02+7/19/99*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. After review and reconsideration, the finality of the Office action of the Paper mailed September 10, 2002 is withdrawn in light of the new grounds of rejection below.

2. Claims 15 and 24-28 are pending and under consideration.

3. Sections of Title 35 U.S. Code not found in this action can be found in a previous action.

4. Claims 15 and 24–28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to the treatment of elevated blood levels of ionized calcium

Claim 15 is drawn to a method of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by Il-6 production, said method comprising administering to said patient a therapeutically effective amount of an antibody to an Il-6 receptor in a pharmaceutically acceptable carrier to suppress elevation of blood level of ionized calcium and wherein the therapeutically effective amount blocks signal transduction by Il-6 and inhibits the binding of Il-6 to the Il-6 receptor.

The specific limitation of "elevated blood level of ionized calcium" was added in an amendment filed August 28, 2001. The specification as filed states on page 2, lines 6-9, that the present invention provides pharmaceutical compositions for the treatment of diseases caused by Il-6 production. On page 3, lines 26-30, the specification states that diseases caused by Il-6 production include plasmacytosis such as rheumatism and Castleman's disease, hyperglobulinemia, anemia, nephritis, cachexia etc. It is noted that no specific mention is made of hypercalcemia as a disease caused by Il-6 production. The specification states (pages 25, line 36 to page 26, line 3, and page 26, line 35 to page 27, last line) that the level of ionized calcium was strongly suppressed in cachexic mice treated with the MR16-1 antibody relative to the non-treated group. This specification does not provide adequate written description for the

amendment which requires the treatment of a patient suffering from elevated blood levels of ionized calcium assoicated with cachexia rather than the treatment of cachexia. One of skill in the art upon reading the specification as filed would not have concluded that the method of treatment was confined to those individuals suffering from cachexia induced hyperglycemia as the specification clearly states the intention of treating cachexia. Further it is recognized in the art that hypercalcemia associated with malignancy is observed in patients who are a few months from death (Potts, J. T. , In: Harrison's Principles of Internal Medicine, 12 Ed., Wilson et al, Ed, 1991, page 1902). Thus, limitation of the treatment to only a subset of patients with cachexia is not supported by the specification or claims as filed, because it restricts the treatment of patients suffering from cachexia to those exhibiting high levels of blood calcium, and said restriction is not supported by the specification or claims as filed.

(B) As drawn to chimeric antibodies.

The specification as filed suggests that antibodies of the invention include MR16-1 and PM-1 (page 14, lines 12-16), and originally filed claims 13 and 14 are drawn to reshaped human antibodies and reshaped human PM-1, respectively. This fails to provide support for the chimeric antibody of claim 24, which encompasses a broader class of antibodies than humanized antibodies.

5. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al (Cancer Research, 1993, vol. 53, pp. 737-740) in view of Shimamura et al (U.S. 5,639,455).

Yoneda et al teach that administration of anti-IL6 antibodies to mice carrying tumors associated with increased production of Il-6 lowered the blood calcium level in said mice (page 738, first column, line 11 under the heading "Results" to column 2, line 2). Yoneda et al did not teach the administration of anti-IL6-receptor antibodies.

Shimamura et al teaches that antibodies to Il-6 or antibodies to the Il-6 receptor can inhibit the binding of Il-6 to the Il-6 receptor. Shimamura et al teach the administration of peptide which inhibit the binding of Il-6 to the Il-6 receptor for the treatment of cancer cachexia (column 9, lines 10-11). Thus, Shimaura et al teaches the treatment of cachexia by the blocking of Il-6 binding to the Il-6 receptor, and teaches that antibodies to the Il-6 receptor can serve to block the binding to Il-6 to the Il-6 receptor.

It would have been prima facie obvious at the time the claimed invention was made to treat hypercalcemia associated with cachexia by administering an anti-Il-6 receptor antibody that blocks the binding of Il-6 to the Il-6 receptor. One of skill in the art would have been motivated to do so by the teachings of Yoneda et al who demonstrate that antibodies which neutralize Il-6 cause a decrease in blood calcium levels in mice suffering from cachexia, and the teachings of Shimamura et al on the treatment of cachexia by peptides which block the binding of Il-6 to the Il-6 receptor and the further teachings of Shimamura et al that anti-Il-6 receptor antibodies can also block the binding of Il-6 to the Il-6 receptor. Thus, one of skill in the art would conclude that the blocking of Il-6 from binding to the Il-6 receptor which was demonstrated by Yoneda et al to lower blood calcium levels could also be carried out by the blocking of Il-6 from the Il-6 receptor using an anti-Il-6 receptor antibody.

6. Claims 15, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al and Shimamura et al as applied to claim 15 above, and further in view of Schwabe et al (Journal of Biological Chemistry, 1994, Vol. 10, pp. 7201-7209).

The combination of Yoneda et al (Cancer Research, 1993, vol. 53, pp. 737-740) in view of Shimamura et al (U.S. 5,639,455) render obvious claims 15 and 24 for the reasons set forth above. Neither reference teaches the PM-1 antibody.

Schwabe et al teach that the anti-Il6 receptor antibody, PM-1, completely inhibited the binding of Il-6 to the Il-6 receptor (page 7204, lines 27-29).

It would have been prima facie obvious at the time the invention was made to use the PM-1 antibody for the treatment of hypercalcemia associated with cachexia. One of skill in the art would have been motivated to do so by the teachings of Schwabe et al on the ability of the PM-1 antibody to block the formation of the Il-6-Il-6 receptor complex.

7. Claims 15 and 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoneda et al and Shimamura et al and Schwabe as applied to claims 15, 24 and 25 above, and further in view of Tsuchiya et al (5,795,965).

The combination of Yoneda et al and Shimamura et al and Schwabe render obvious the limitations of claims 15, 24 and 25 for the reasons set forth above. The combination does not teach a chimeric or humanized antibody.

Tsuchiya et al teaches the chimeric and reshaped human PM-1 antibody for therapeutic purposes (column 7, lines 21-37, column 46, lines 59-67 and claim 6). Tsuchiya et al teaches that mouse antibodies are highly immunogenic in humans and therefore cannot be administered in multiple doses without generating an immune response which interferes with the planned efficacy of the administered antibody (column 1, lines 52-59). Tsuchiya et al teaches a reduction in immunogenicity by using chimeric (column 1, line 60 to column 2, line 9) and humanized (column 2, lines 10-22).

It would have been prima facie obvious at the time the invention was made to use the chimeric or reshaped humanized antibody to PM-1 in the invention rendered obvious by the combination of Yoneda et al and Shimamura et al and Schwabe. One of skill in the art would have been motivated to do so by the teachings of Tsuchiya et al on the decrease in immunogenicity afforded by both the chimeric and humanized antibodies.

8. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/12/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER